REMARKS

This paper is filed in response to the final official action dated October 14, 2008 (hereafter, the "official action"). This paper is timely filed as it is accompanied by a petition for extension of time and authorization to charge our credit card account in the amount of the requisite fee. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith to our Deposit Account No. 13-2855, under Order No. ANA-5955 (31203/30056).

Claims 1, 2, 4, 5, and 7-13 are pending in this application. All pending claims 1, 2, 4, 5, and 7-13 have been rejected under 35 U.S.C. §103(a) as assertedly obvious over Saito *et al.*, *J. Cerebral Blood Flow Metabol.*, *17*:857-864 (1997) ("Saito") in view of Gray *et al.*, GB 2350297 ("Gray") and Gelb *et al.*, *Canadian Anaesth. Soc. J.*:*25(6)*:488-494 (Nov. 1978). The applicants respectfully traverse the rejections.

Saito discloses administering to cats, via inhalation, 0.75% halothane in 70% nitrous oxide and 30% oxygen, which corresponds to an amount of halothane sufficient to maintain a general anesthetic effect (as demonstrated by Toyota *et al.*, *Stroke*, *33*:1383-1391 (2002), which was enclosed with applicants' previous response). Saito further suggests that the aforementioned halothane administration provided some protective effect against left middle cerebral artery occlusion- induced brain ischemia.

All pending claims recite a method of treating a patient having a tissue that is subject to an ischemic event comprising *parenterally administering* a formulation comprising a halogenated volatile anesthetic to the patient *in a sub-anesthetic amount* effective to improve the tissue's resistance to or tolerance of the ischemic event. The examiner acknowledged that "Saito et al do not teach parenteral administration of a halogenated volatile anesthetic, with an emulsification adjuvant and an emulsifier in a sub-anesthetic amount." *See* pages 6-7 of the official action.[1]

Thus, the examiner turned to Gray, which discloses an injectable halogenated anesthetic formulation, and Gelb, which discloses administration of sub-anesthetic amounts of halothane. The proposed combination of Saito with Gray and/or Gelb, however, is flawed for at least the following reasons.

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[1] The examiner's characterization of Saito as teaching "an anesthetic [that] can be administered as an injectable bolus or as an infusion for continuous anesthetic administration" is entirely misplaced as the anesthetic administered as an injectable bolus and as an infusion (alpha-chloralose) showed no protective effect against ischemic insult and thus is entirely relevant to the claimed subject matter.

The reasoning necessary to sustain the proposed combination of Saito with Gray and Gelb requires that the halothane administered by inhalation in Saito and the injectable formulation disclosed in Gray produce substantially equivalent protective effects against ischemic insult. The applicants respectfully submit that one of ordinary skill would not have a reasonable expectation that the protective effect described in Saito, which was achieved via inhalation administration of halothane, could also be achieved by parenterally administering a formulation comprising a halogenated volatile anesthetic (such as halothane), as claimed. In fact, it is well known that one cannot presume that different routes of administration (of the same drug) achieve the same physiological effect. In this regard, the examiner is respectfully directed to Lucchinetti, *et al.*, *Int'l Anesthesia Res. Soc.*, *106(5)*:1346-1349 (May 2008),[2] which unequivocally states:

> ...the route of administration are known to profoundly affect pharmacokinetic and/or dynamic properties of a drug, to modify the ratio between therapeutic activities versus toxicity (therapeutic index), and are even capable of evoking novel biological actions.

In view of the understanding in the art that there are profound differences attributable to different routes of administration, the rationale necessary to sustain the proposed combination of Saito with Gray and Gelb does not have an appropriate foundation, but rather results from impermissible hindsight reconstruction. Accordingly, the rejections should be withdrawn.

Moreover, Gray discloses injectable halogenated anesthetics for *inducing* an anesthetic effect. Saito discloses using halothane as an agent for maintaining a general anesthetic effect. Therefore, one of ordinary skill would not look to the inducing anesthetic composition of Gray to modify the maintaining anesthetic composition of Saito.

Furthermore, the reasoning necessary to support the proposed combination of Saito with Gray and Gelb requires that one of ordinary skill in the art would have an expectation that the protective effect described in Saito, which was achieved via inhalation administration of an anesthetic amount, could also be achieved by administering a sub-anesthetic amount, as claimed. Saito, however, explicitly indicates that any ischemic protective effect demonstrated therein is limited to administering an *anesthetic amount* of halothane by distinguishing between the awake and anesthetized states:

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[2] The document is attached hereto as Attachment A.

> *Compared with the awake state*, volatile anesthetics, including halothane and sevoflurane, reduce brain damage in animals subjected to transient focal cerebral ischemia.

See Saito at page 862 (emphasis added). Therefore, one of ordinary skill in the art would not separate the protective effect demonstrated in Saito from the induced anesthetic state, as proposed by the examiner.

The applicants recognize that the examiner also suggested at page 3 of the action that "it is well within the purview of the skilled artisan to optimize the dosage of the anesthetic agent to discover the optimum concentration of the anesthetic for use in such method." In *re* Antonie, 559 F.2d 618 (CCPA 1977) provides that "[a] particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." As mentioned above, Saito fails to provide *any recognition* that the dosage should (or even could) be varied by distinguishing between the awake and anesthetized states. Thus, Saito fails to contemplate or suggest any dosage other than an anesthetic amount and its combination with Gelb is improper.

Furthermore, Gelb merely discloses that halothane administration reduces the ventilatory response in a dose-dependent fashion. It is not at all clear why one of ordinary skill would be motivated to substitute a sub-anesthetic amount of a halogenated anesthetic for an anesthetic amount based on the teachings of Gelb.

For at least the foregoing reasons, a *prima facie* case of obviousness cannot be sustained.

CONCLUSION

It is respectfully submitted that this application is now in condition for allowance. Should the examiner wish to discuss the foregoing, or any matter of form or procedure in an effort to advance this application to allowance, the examiner is respectfully invited to contact the undersigned attorney at the indicated telephone number.

Respectfully submitted,

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